Leukotriene Inhibitors [Montelukast (marketed as Singulair), Zafirlukast (marketed as Accolate), and Zileuton (marketed as Zyflo and Zyflo CR)] and Neuropsychiatric Events

- In April 2009, the Food and Drug Administration (FDA) reviewed post-marketing reports and clinical trial data on mood and behavioral changes associated with the use of leukotriene inhibitors.  
- Neuropsychiatric events reported in patients taking montelukast (Singulair), zafirlukast (Accolate), and zileuton (Zyflo and Zyflo CR) include:
  - Agitation
  - Aggression
  - Anxiousness
  - Dream abnormalities and hallucinations
  - Depression
  - Insomnia
  - Irritability
  - Restlessness
  - Suicidal thinking and behavior (including suicide)
  - Tremor.
- FDA has requested that manufacturers revise the drug prescribing information to include a precaution addressing the above events.
- Limited literature exists regarding suicidality and leukotriene inhibitors.  
  - One study reviewed available reports of suicidality and treatment of allergy with leukotriene inhibitors and found insufficient data associating montelukast with suicidality.  
  - Another population-based cohort study showed no cases of suicide in patients receiving montelukast during the study time period.  
    - 23,500 patients received over 250,000 montelukast prescriptions from February 1998 – March 2007.  
    - No cases of suicide were identified.
- FDA recommends:
  - Patients and healthcare professionals should be aware of the potential for neuropsychiatric events with these medications.
  - Patients should talk with their healthcare providers if these events occur.
  - Healthcare professionals should consider discontinuing these medications if patients develop neuropsychiatric symptoms.
- VA Center for Medication Safety (VAMedSAFE) will monitor and analyze reports of adverse events with leukotriene inhibitors to better characterize the adverse event profile in the veteran population.

REFERENCES:

ACTIONS
- **Facility Director (or physician designee):** Report completion of actions to the VISN Director.
- **Facility COS and Chief Nurse Executives:** Forward this document to all appropriate providers who prescribe/use/handle this agent (e.g., primary care providers, pulmonologists, allergy-immunology providers, and head and neck surgeons, including contract providers, etc.). In addition, forward to the Associate Chief of Staff (ACOS) for Research and Development (R&D). Forward to other VA employees as deemed appropriate. Report completion of actions to the Facility Director.
- **ACOS for R&D:** Forward this document to Principal Investigators (PIs) who have authority to practice at the facility and to your respective Institutional Review Board (IRB).
- **VISN Directors:** Within 10 business days of receipt (due 06/29/2009), communicate to PBM/VAMedSAFE that all actions have been completed via the Feedback tool: http://vawww.national.cmop.va.gov/PBM/visn_drug_recalls_alerts/default.aspx.